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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,725	11/30/2001	Wely B. Floriano	06618-607002	4307
7590 10/15/2003				
SCOTT HARRIS Fish & Richardson P.C. Suite 500 4350 La Jolla Drive San Diego, CA 92122				
EXAMINER LY, CHEYNE D				
ART UNIT		PAPER NUMBER		
1631				

DATE MAILED: 10/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,725	FLORIANO ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on July 28, 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-35 is/are pending in the application.
- 4a) Of the above claim(s) 17-28 and 30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16, 29 and 31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-35 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's election without traversal of Group I, claims 1-16, 29, and 31, filed July 28, 2003, is acknowledged.
2. Claims 1-16, 29, and 31 are examined on the merits.

OBJECTIONS

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (Page 17, Lines 6). Applicant(s) is/are required to delete the embedded hyperlink and/or other form of browser-executable code, or inactivate the hyperlink. See MPEP § 608.01.

CLAIM REJECTIONS - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
5. Claims 1-16, 29, and 31 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.
6. Claims 1-16, 29, and 31 are rejected due to the claimed subject matter being directed to a non-statutory subject matter due to lacking any physical steps such as displaying the stored information from a computer. Currently, the steps are merely algorithmic processes of manipulating data directed to ligand-protein binding interactions without providing a means of visualizing the results of the said processes; therefore, the claim subject matter lacks a real world value. The claimed invention as a whole is directed to a combination of interrelated elements, which combine to form a machine for storing ligand-protein binding interactions in a computer without providing a means for displaying the stored data directed to ligand-protein binding

Art Unit: 1631

interactions. The critical steps of displaying the drug information would cause the subject matter in its entirety to be a practical application (MPEP § 2106 (IV)(B)(2) (b)).

7. It is acknowledged that the instant claims recite a limitation wherein data directed to ligand-protein binding interactions are outputted, which could be reasonably interpreted as simply storing the results in a computer file.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-16, 29, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Specific to claims 1, lines 7, 9, 13, and 16-17; 29, line 4; and 31, lines 9 and 11; the phrase “preferred binding conformations” causes the claims to be vague and indefinite because it is unclear what criteria are being used to considered a conformation to be a “preferred binding conformation” (spatial clustering or having certain percentage of ligand surface area buried in a protein). Clarification of the metes and bounds of the claims is required. Claims 2-16 are rejected for being dependent from claim 1.

11. Specific to claim 4, line 11; 5, lines 2-3; 6, lines 2-3 and 7; 7, line 6; and 8, lines 2 and 3; the phrase “best conformations” causes the claims to be vague and indefinite because it is unclear what criteria are being used to considered a conformation to be the “best conformation” (spatial clustering or having certain percentage of ligand surface area buried in a protein). Clarification of the metes and bounds of the claims is required.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-16, 29, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method and computer program for modeling ligand-protein binding interactions based on crystal structures Phenylalanyl t-RNA synthetase (Example 1), histidyl t-RNA synthetase (Example 2), OR S25 (Example 3), OR S18 (Example 4), and retinal in bovine rhodopsin (Example 5) protein ligand interactions, does not reasonably provide enablement for any protein ligand interaction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

15. It is acknowledged that the applicant has disclosed information to enable one skilled in the art to practice the claimed method based on crystal structures of Phenylalanyl t-RNA (Example 1), histdyl t-RNA (Example 2), OR S25 (Example 3), OR S18 (Example 4), or retinal in bovine rhodopsin (Example 5) protein ligand interaction. Further, Applicant discloses that the claimed method and computer program rely on the crystallographic data from PDB or Cambridge Structural Database (pages 15-16, Figure 1). However, a method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said method. It is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002). Accordingly, it would be unpredictable for one skilled in the art to practice the claimed invention with any other protein beyond the ones of the instant case. In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the information disclosed for Phenylalanyl t-RNA (Example 1), histdyl t-RNA (Example 2), OR S25 (Example 3), OR S18 (Example 4), and retinal in bovine rhodopsin (Example 5) to practice said invention with any other protein without undue experimentation.

Claim Rejections - 35 USC § 102

Art Unit: 1631

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

2. Claims 1-16, 29, and 31 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Zou et al. (1999).

3. Zou et al. discloses a method and computer program for modeling ligand receptor binding interactions wherein structural information based on solvation effects for said receptors are derived from crystal structures to identify binding regions (page 8037, columns 1-2, III. Results, § 1). A 10 best scoring results (output) according to free energy calculations for a plurality of conformations are discloses in Table 4. The binding energy calculations are optimized in ordered to rank inhibitors correctly (page 8037, column 1, § 6. Optimization for the Parameter Set), as in instant claim 1.

4. The crystal structures used for identifying binding regions are derived from dhfr-MTX (page 8037, columns 2, lines 3-5), as in instant claim 2.

5. The step of optimization for the parameter set is directed to known and unknown binding regions for predicting binding energies (page 8037, column 1, § 6. Optimization for the Parameter Set), as in instant claim 3.

6. Zou et al. discloses the treatment of solvent molecules in molecular dynamics simulations (page 8033, column 2, lines 14-15), unoccupied embedded space between ligand and the receptor (empty volume) is penalized in the said method (Abstract etc.), and energy minimization is

performed with DOCK force field (page 8037, column 2, lines 14-17 and Table 1), as in instant claims 4-9.

7. Zou et al. discloses a simple solvation model uses atom or group-based solvent exposed area terms; and an approach wherein the solvent is treated as a continuum dielectric medium (page 8034, column 1, lines 12-13), as in instant claims 10 and 11

8. The binding energy for each ligand is calculated by taking the difference in the ligand energy of ligand in solvent and in receptor (page 8035, columns 2, § 3 and § 4 to page 8036, column 1), as in instant claim 12.

9. The method of Zou et al. is directed to globular protein and the calculation of dielectric constant of said protein in water (page 9035, column 1, lines 3-12), as in instant claims 13-16.

10. The method of Zou et al. is implemented using a Silicon Graphics R1000 workstation for generating ligand receptor binding models (Abstract etc. and Figures 3 and 4), as in instant claims 29 and 31.

CONCLUSION

11. NO CLAIM IS ALLOWED.

12. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Art Unit: 1631

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

14. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

15. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
10/9/03


ARDIN H. MARSCHEL
PRIMARY EXAMINER